

General

Guideline Title

NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents.

Bibliographic Source(s)

Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, Rosenthal P, Schwarz KB. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr.* 2012 Jun;54(6):838-55. [176 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of the recommendations (Grading of Recommendations Assessment, Development, and Evaluation [GRADE]: 1, 2 and International Maternal Pediatric Adolescent AIDS Clinical Trial [IMPAACT]: A, B, C) and the quality of the evidence (GRADE: A, B, C and IMPAACT: I, I*, II, II*, III) are defined at the end of the "Major Recommendations" field.

Diagnosis

Whom to Test for Hepatitis C Virus (HCV)

Testing is indicated in individuals at risk for HCV infection as outlined in the table below ("Recommendations," 1998). A special mention is merited for investigation of mother-to-infant transmission of HCV. Because anti-HCV immunoglobulin G (IgG) crosses the placenta, testing anti-HCV is not informative until the infant is 18 months old, at which time antibody testing should be performed (England et al., 2005). Patients older than 18 months with positive anti-HCV IgG should have subsequent testing for serum HCV ribonucleic acid (RNA) to determine active infection. If requested by the family, the serum HCV RNA can be tested before 18 months of age; however, infants should be at least 2 months old (Polywka et al., 2006). If serum HCV RNA is positive in early infancy, it should be rechecked after 12 months of age to determine presence of chronic hepatitis C (CHC).

Table: Persons for Whom Screening for HCV Infection is Indicated

Group	Screening
Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users	Antibody

Group	Screening
Persons with conditions associated with a high prevalence of HCV infection including: <ul style="list-style-type: none"> • Persons with human immunodeficiency virus (HIV) infection • Persons who have ever been on hemodialysis • Persons with unexplained abnormal aminotransferase levels 	Antibody or RNA
Earlier recipients of transfusions or organ transplants before July 1992 including: <ul style="list-style-type: none"> • Persons who were notified that they had received blood from a donor who later tested positive for HCV infection • Persons who received a transfusion of blood or blood products • Persons who received an organ transplant 	Antibody or RNA
Children born to HCV-infected mothers	Antibody after 18 months of age, RNA for younger ages
Health care, emergency medical, and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood	Antibody or RNA
Present sexual partners of HCV-infected persons	Antibody
Children with chronically elevated transaminases	Antibody
Children from a region with high prevalence of HCV infection	Antibody

Note: All of the positive anti-HCV antibody tests should be followed up with an HCV RNA test to determine active infection.

Adapted from: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease, Control and Prevention. MMWR Recomm Rep 1998;47 (RR-19):1–39.

Diagnostic Tests

Antibody-Based (IgG)

The available tests are immunoassays, which are easy to perform, automated, characterized by low variability, and relatively inexpensive. For these reasons, antibody-based tests are generally recommended for screening; however, they should not be used in infants younger than 18 months given the likelihood of reactivity due to maternal antibody (American Academy of Pediatrics, 2006). There are 3 types of immunoassays: enzyme immunoassay (EIA), microparticle EIA, and chemiluminescence immunoassay.

Supplementary Table 1 (<http://links.lww.com/MPG/A112>) lists the Food and Drug Administration (FDA)–approved antibody-based assays. The first 2 are recommended for screening and use a mixture of proteins as the solid-phase agent. The third can be used for supplemental testing for detection of antibodies to individual HCV proteins.

Another antibody-based test of interest, the OraQuick HCV rapid antibody test, was approved by the FDA in June 2010. It uses whole blood samples obtained by venipuncture. The major advantage of this test is that it allows point-of-care testing in that it is portable and easy to use; it provides an answer within 40 minutes and can therefore be used for HCV screening for persons who are at risk for hepatitis, such as youths who live on the streets or are incarcerated (Lee et al., 2010; Lee et al., 2011). Further testing is necessary to confirm HCV infection if the test result is positive. Anti-HCV immunoglobulin M (IgM) is not useful for distinguishing between acute and chronic HCV infection and measuring HCV IgM is not recommended.

Qualitative and Quantitative HCV RNA

Supplementary Table 2 (<http://links.lww.com/MPG/A112>) summarizes the FDA-approved qualitative and quantitative tests for HCV RNA, usually performed by reverse transcriptase-polymerase chain reaction (RT-PCR). In the past, qualitative tests were used for diagnosis because they were more sensitive than the quantitative tests. Recently improved to be greatly sensitive, quantitative tests are now recommended for diagnosis in patients with positive anti-HCV antibody tests (Ghany et al., 2009).

See the original guideline document for the interpretation of the HCV RNA tests and antibody tests. HCV RNA tests can be detected in serum or plasma as early as 1 to 2 weeks after exposure to the virus and weeks before the antibody tests become positive or the liver enzymes become elevated (Mukherjee, Lin, & Bronze, 2011).

HCV Genotypes

IL28B receptor testing may be considered for children with genotype 1 before embarking on therapy because IL28B receptor variants have been

quite useful for predicting response to pegylated interferon alfa (PEG-IFN- α) and ribavirin in adults with genotype 1 (Halfon et al., 2011).

Monitoring and Anticipatory Guidance

Monitoring of Children Who are Treatment Naive

Children with chronic HCV infection not receiving antiviral therapy should be evaluated annually to provide ongoing education and to assess for clinical and biochemical evidence of chronic liver disease. Laboratory investigations during periodic assessments may include serum aminotransferases, bilirubin (total and direct/conjugated), albumin, HCV RNA levels, complete blood count (with platelet count), and prothrombin time/international normalized ratio (if cirrhosis is present) (2A; BII). Liver biopsy should be generally considered only if the result will influence medical decision making. Liver biopsy may be specifically useful to investigate unexplained clinical hepatic decompensation in a previously stable patient and in children who are being considered for antiviral treatment to assess severity of liver disease. It is reasonable to forgo pretreatment liver biopsy in children with HCV genotypes 2 or 3 who have a high (>80%) probability of achieving a virological cure with presently available treatments (see below) (2B; BII).

Screening for Hepatocellular Carcinoma

As noted above, there are only a few reported cases of children with chronic HCV infection developing hepatocellular carcinoma (HCC) (Gonzalez-Peralta et al., 2009; Strickland, Jenkins, & Hudson, 2001). In those with significant liver disease (i.e., cirrhosis), abdominal ultrasonography and serum α -fetoprotein should be considered annually or biannually for surveillance of HCC (2B; BII*).

Monitoring of Children Younger Than 3 Years with HCV Infection

Vertical transmission presently accounts for the majority of pediatric HCV infections. Children born to HCV-infected mothers should be screened for CHC with anti-HCV antibody testing at 18 months of age, when maternally derived antibodies have cleared (1B; AIII); however, sensitive nucleic amplification assays to detect HCV RNA may be useful in selected cases where the potential of having transmitted an infection results in significant maternal anxiety, despite the low risk of transmission (Yeung, King, & Roberts, 2001) (2B; BIII). In this particular setting, the early exclusion of HCV infection is reassuring and may be worth the added expense. Of note, infants with detectable HCV RNA in infancy should be periodically monitored because spontaneous viral clearance may occur during childhood, particularly in HCV genotype 3 infections (Guido et al., 1998).

Anticipatory Guidance and Screening

Present evidence does not support routine screening of household contacts (2B; BIII). One exception is that in the setting of known vertical transmission, siblings should be screened for vertical transmission of HCV infection as well. Children, caregivers, and their families exposed to HCV-infected patients require effective education on avoidance of virus acquisition as outlined in the table "Anticipatory Guidance and Screening" below (1A; AIII) (Tohne & Holmberg, 2010; Larzo & Poe, 2006; Daniel & Shehab, 2005). Adult data have shown an increase in transmission with multiple sexual partners, although the risk of transmission is between 1% and 5% in monogamous relationships. Indirectly, spouses of HCV-positive index cases have a greater risk of becoming infected. Children with CHC are encouraged to lead normal lives. Nonetheless, special situations need appropriate handling as delineated in the table "Special Considerations for Pediatric HCV Infection" below (Baizhanova, Ignatova, & Nekrasova, 2010; Hwang & Lee, 2011; Peters & Terrault, 2002; Rose, 1998; Pembrey, Newell, & Tovo, 1999; European Paediatric Hepatitis C Virus Network [EPHN], 2001; EPHN, 2005; Lin et al., 1995; Resti et al., 2000; Mok et al. 2005).

Table: Anticipatory Guidance and Screening

Category	No Contraindication	Avoid	Routine Screening
Household contacts	Sharing food, drink, eating utensils, clothes, towels, laundry, toilet seats (1A; AIII)	Sharing toothbrush, shaving equipment, nail clippers, tweezers, glucometers, or other personal item that may be contaminated with blood	Not recommended (2B; BIII)
Nonhousehold contacts	Attending day care, school, camps, playgrounds, play dates, community pools; participating in contact and non-contact sports	N.A.	Not recommended (2B; BIII)
Casual contacts	Kissing, hugging, holding hands	N.A.	Not recommended (2B; BIII)
Sexual contacts	Monogamous sexual contact	Unprotected sexual activity with multiple partners (Tohne & Holmberg, 2010)	Not recommended: monogamous relations;

Category	No Contraindication	Avoid	Recommended: polygamous relations (2B; BIII) Routine Screening
Other activities	N.A.	Tattooing (Larzo & Poe, 2006), body piercing (Daniel & Shehab, 2005)	N.A.

N.A. = Not applicable

Table: Special Considerations for Pediatric HCV Infection

Special Situation	Recommendations
Blood spills (including dried blood)	Thoroughly clean spill area using a dilution of 1 part household bleach to 10 parts water. Gloves should be worn when cleaning up blood spills (refer to www.CDC.gov <input type="text"/>).
Minor cuts or bruises	Observe universal precautions.
Use of over-the-counter analgesia, anti-inflammatory and antipyretics	Occasional use is acceptable. NSAIDs should be avoided in those with varices. Short intermittent courses of corticosteroids such as for asthma are acceptable.
Vaccinations	Should receive all of the age-appropriate immunizations, including hepatitis A and hepatitis B vaccines (1A; AI*)
Obesity	Obesity may further burden liver health and negatively influence response to HCV therapy (Baizhanova, Ignatova & Nekrasova, 2010; Hwang & Lee, 2011).
Exercise	No restrictions to school and sports
Alcohol consumption	Avoid alcohol consumption because it strongly correlates with rapid progression of liver disease (Peters & Terrault, 2002).
Illicit drug use (nasal cocaine, intravenous agents)	Avoid high-risk behaviors that will promote HCV reinfection (posttreatment) and transmission of other viruses.
Pregnancy	Because there are presently no effective strategies to prevent perinatal HCV transmission, universal screening of pregnant women is not recommended (Rose, 1998).
Obstetrical-perinatal factors	Vertical transmission of HCV is similar between infants born by C-section or vaginally; however, prolonged rupture of membranes and the use of fetal scalp probes are associated with increased HCV transmission rates and should be avoided (1B; AII) (Pembrey, Newell & Tovo, 1999; EPHN, 2001; EPHN, 2005).
Postnatal period	The rate of vertical transmission is similar between breast- and bottle-fed infants. Hence, breast-feeding is not generally contraindicated in mothers with HCV infection. Breast-feeding should be avoided if there is mastitis or bleeding (1B; AII) (Lin et al., 1995; Resti et al., 2000; Mok et al. 2005).

HCV = Hepatitis C virus; NSAIDs = Nonsteroidal anti-inflammatory drugs

Disclosures

Disclosing HCV infection to day-care personnel, school teachers and school personnel, sports coaches, authorities, peers, and casual dates can be a contentious and anxiety-provoking proposition. Although there likely are national and international geographic regulations with regards to this issue, there is generally no legal requirement to disclose HCV infection to casual or sexual contacts in the United States; however, the Centers for Diseases Control and Prevention (CDC) and many patient advocate groups suggest revealing this information to sexual partners when appropriate (www.hcvadvocate.org ; www.cdc.gov/hepatitis/hcv). This recommendation poses further ethical concerns and questions regarding the appropriate timing to disclose this information and how it should be done. This decision should be individualized and should be arrived at only after thoroughly weighing all of the advantages and disadvantages of transmitting this information, largely based on the cognitive development of the individuals involved. Further information can be obtained from the HCV Advocate website (<http://hcvadvocate.org>).

Treatment of Hepatitis C

There are several schools of thought regarding the need for treatment of children with CHC. Because CHC generally has a slow progression to fibrosis and severe disease is rare in children, follow up without treatment until adulthood may be a valid option for many children. Treatment during childhood does not achieve increased rates of response compared with adults, and adverse events are frequent and in some cases, may be

severe. Conversely, treatment may be justified because it allows definitive resolution in a subgroup of patients. Adolescence and young adulthood are associated with busy school and work demands, which may result in a lack of compliance with medical regimens and visits. All of those factors may lead to postponed treatment. Conversely, treatment of young children may be accomplished more easily given motivated caregivers and schedules, which can be more easily adjusted to therapeutic regimens than is the case for adolescents.

Children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e., fibrosis on liver histology) should be considered for treatment.

The goals of treatment in the individual patients are eradicating virus infection, preventing end-stage liver disease and HCC, and removing stigma associated with HCV infection. An overall goal is to decrease the global burden of disease. Presently available treatments for pediatric CHC are IFN- α or PEG-IFN- α and ribavirin. The American Association for the Study of Liver Diseases (AASLD) recommends the FDA-approved combination of PEG-IFN- α with ribavirin as first-line treatment for CHC in adults and children ages 3 to 17 years (Ghany et al., 2009) (1A; AI). See the original protocol document for further discussion of treatment regimens.

The recommended length of therapy is 48 weeks of treatment for genotypes 1 or 4 and 24-week duration of treatment for genotypes 2 or 3 in children (1A; A1*). If HCV RNA does not become undetectable by 24 weeks, there is also no evidence that prolonged treatment improves clinical outcome (i.e., cirrhosis, HCC, sustained viral response [SVR]) (Di Bisceglie et al., 2008).

Side Effects of Medications and Monitoring for Adverse Events

IFN- α and ribavirin are powerful medications that are associated with multiple potential side effects and adverse events that affect quality of life (Sung, Chang, & Saab, 2011; Foster, 2009). A thorough understanding of side effects is essential to intervene in a timely fashion and to avoid severe adverse events. Caretakers need to educate the patient and family on the necessary monitoring for side effects.

The incidence of side effects associated with PEG-IFN- α and ribavirin therapy for pediatric CHC is shown in Table 7 of the original guideline document, and recommendations on monitoring for side effects are outlined in the table below. Constitutional symptoms are almost universal in children undergoing therapy. These symptoms include fever, fatigue, myalgias, arthralgias, headaches, and nausea. With the exception of nausea, these constitutional complaints are predominantly side effects of IFN- α . The constitutional symptoms are usually most severe within 24 hours of the IFN injection, and many symptoms will wane or resolve after the first few months of therapy (Wirth et al., 2005; Sung, Chang & Saab, 2011).

The pediatric population is uniquely susceptible to deficits in growth in both weight and height while receiving PEG-IFN- α and ribavirin. Both PEG-IFN- α and ribavirin can be associated with anorexia, nausea, and subsequent weight loss. Long-term follow-up of growth parameters is necessary to determine whether the growth inhibition is temporary or long-lasting.

Bone marrow suppression induced by IFN- α constitutes the next most common toxicity after constitutional symptoms, occurring in approximately one third of treatment recipients (Schwarz et al., 2011; Wirth et al., 2010). The bone marrow toxicity is associated with depressed levels of total white cell and absolute neutrophil counts, and, to a lesser extent, platelets and red cells. The neutropenia usually reaches a sustained nadir by 8 weeks of therapy and returns to baseline within weeks after cessation of therapy (Schwarz et al., 2011; Abdel-Aziz et al., 2011).

IFN- α -induced reductions in platelet counts are usually asymptomatic and manifest within the first 8 weeks of therapy. Platelet levels then stabilize at this lower level for the duration of therapy (Sung, Chung & Saab, 2011).

Ribavirin is the main contributor to the onset of hemolytic anemia that most commonly manifests in the first month of treatment, reaching a nadir by week 4 (Sung, Chung & Saab, 2011; Abdel-Aziz et al., 2011).

Dose adjustments may be insufficient to ameliorate marrow suppression, and interventions to treat severe or symptomatic anemia or neutropenia may be necessary (Collantes & Younossi, 2005). Available agents include Epogen (epoetin alfa, Amgen Inc, Thousand Oaks, CA) for anemia, granulocyte colony stimulating factor (G-CSF) for neutropenia, and blood products.

IFN-associated neuropsychiatric complications can be the most challenging to manage during treatment for CHC. IFN- α therapy has been associated with the initiation or worsening of underlying depression, anxiety, and suicidal ideation (Al-Huthail, 2006). It is essential to perform a baseline neuropsychiatric evaluation and specifically to survey for signs of depression before initiation of therapy. The onset of neuropsychiatric symptoms may not occur until 3 to 6 months into therapy (Sung, Chang, & Saab, 2011). It is recommended that whenever there is a concern for major depression or other psychiatric illnesses, the child should be referred to a psychiatrist for consideration of initiating antidepressant therapy or discontinuing IFN- α therapy. Discontinuation of therapy is strongly recommended in the setting of suicidal ideations or attempted suicide.

Thyroid abnormalities are the most common endocrinological adverse effect induced by IFN- α , occurring in 1% to 6% of adults treated with IFN- α (Sung, Chang, & Saab, 2011). Thyroid abnormalities can occur at any time during therapy. It is recommended that thyroid-stimulating hormone (TSH) and total T4 levels be measured every 3 months during therapy. The diagnosis of clinical hypothyroidism should be confirmed and

subsequently managed by an endocrinologist. Similar to the autoimmune-mediated mechanism of thyroid injury, antibodies to the adrenal cortex or pancreatic islet cells can result in IFN-induced adrenal insufficiency or diabetes, respectively.

A wide variety of ocular complications can occur while receiving IFN- α therapy, such as retinopathy, optic neuritis, or neuropathy. It is recommended that visual disturbances or complaints while receiving therapy warrant expeditious evaluation by an ophthalmologist.

Numerous cutaneous drug reactions can occur, including IFN-induced injection site reactions, dry skin, pruritus, and alopecia. Furthermore, ribavirin can induce a rash characterized by a diffuse inflammatory, erythematous, and maculopapular lesion that resolves after stopping ribavirin (Veluru et al., 2010). The dry skin may mimic eczematous or psoriatic lesions (Mistry, Shapero, & Crawford, 2009).

Finally, another potential complication of CHC treatment is that ribavirin (and to a lesser extent, IFN- α) is greatly teratogenic (Ward & Kugelmas, 2005). Therefore, a urine human chorionic gonadotropin test is recommended for all of the females 13 years or older at baseline and should be repeated at 24 weeks of therapy. Ribavirin can cause teratogenesis when either partner is taking it. In sexually active teenagers, the use of and strict adherence to contraception is mandatory.

In summary, conscientious and thorough monitoring for potential adverse events is essential to optimize care of pediatric patients being treated for CHC. Overall, cessation of therapy due to adverse events is rare and side effects can be managed with appropriate referral care and treatment when necessary.

Table: Recommendations for Monitoring During Therapy

Laboratory Test to Be Monitored	Obtain Test on Following Week of Therapy
CBC with differential, absolute neutrophil count	0, 1, 2, 4, 8, 12 and every 4–8 wk thereafter
Hepatic panel, glucose	0, 1, 2, 4, 8, 12 and every 4–8 wk thereafter
TSH/total T4	0, 12, 24, 36, 48
Urine HCG (for female patients 13 y or older)	0, 24
Prothrombin time	0; only repeat if clinically indicated
Urinalysis	0; only repeat if clinically indicated
HCV RNA	0, 24, 48, 72

CBC = Complete blood count; HCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; RNA = Ribonucleic acid; TSH = Thyroid-stimulating hormone; wk = Week(s)

Special Populations and Outcomes

Individualization of therapy warrants serious consideration under several circumstances. There is a paucity of both data and adequately powered clinical trials in these unique pediatric groups that may warrant therapy for HCV infection.

Young Age

Children who are younger than 3 years should generally not be treated, and treatment is not approved in this age group. In young children, HCV infection may still spontaneously resolve and adverse effects of IFN- α in extremely young children are not well elucidated, although spastic diplegia has been reported in infants treated with IFN- α for hemangiomas (Barlow et al., 1998). There are no published studies or reports of treatment in children who are younger than 3 years. The decision to treat should consider several aspects including age, severity of disease, efficacy of the chosen therapy, its adverse effects, compliance to treatment, and willingness to be treated.

History of Substance Abuse

In general, patients are excluded from therapy if they have severe comorbid medical conditions that could compromise the tolerability of the drugs or interfere with compliance to the regimen. Adolescents and young adults with a history of substance abuse may fall into this category. Adolescents with a history of substance abuse may be candidates for therapy on an individualized basis.

Psychiatric Illness

Treatment for CHC is well known to have multiple neuropsychiatric side effects including depression, confusion, mania, psychosis, hallucinations, and suicidal ideation. There is also risk that a patient's known psychiatric disorder will flare or become unmanageable once therapy is initiated. Psychoeducation groups have shown promise for preparing patients with chronic medical illness to anticipate and endure intensive medical treatment that has substantial psychiatric side effects (Hong et al., 2011). The goal is to aid patients to overcome barriers to treatment, particularly

psychosocial problems, because available CHC treatments have become increasingly effective. Clearance by an appropriately trained psychiatrist for therapy is advisable before commencing treatment. Ongoing psychiatric evaluation and therapy are appropriate during CHC treatment, allowing for either prompt intervention or discontinuation of treatment should severe neuropsychiatric side effects develop.

Juvenile Detention Center Resident

Arguments in favor of treatment for CHC in these individuals include prominently that the patients are a captive audience and much more likely to be compliant with medications, laboratory studies, and visits; however, these individuals are often not incarcerated for the entire length of time required for HCV treatment, and when released may not have the finances or resources to continue therapy.

Coinfection: HIV

Limited experience in the clinical management of this group and the lack of evidence to guide policy are barriers to achieving optimal care and treatment for this special population. If therapy for CHC is initiated, extremely close monitoring for adverse events is necessary.

Coinfection: HBV

If a decision is made to treat an HBV/HCV coinfecting child, combination of PEG-IFN- α and ribavirin for a full course, independent of genotype, is recommended based upon adult data.

Patients with Hematological Disorders Who Have Undergone Multiple Blood Transfusions

The majority of children in this special population will have hemolytic conditions such as sickle cell anemia and thalassemia. The risk of acquiring HCV infection is dependent upon the number of units of blood exposure; however, these risks have declined with the introduction of universal HCV screening of blood products that began in the 1990s. The risk of hemolysis due to ribavirin makes combination therapy a complicated issue. Multiple transfusions are associated with hepatic iron overload, which complicates therapy for CHC and may accelerate the progression of cirrhosis and risk for HCC. Treatment may be effective but the issues of hemolysis with ribavirin, use of injections, and iron overload all need to be considered in the decision to treat (Harmatz et al., 2008).

Transplantation (Renal or Liver)

CHC remains the leading indication for liver transplantation in adults in the United States. After liver transplant, graft reinfection is almost universal and development of chronic HCV, cirrhosis, and death occurs in about one third of adult liver transplant recipients (Ferrell et al., 1992). The risk of HCV recurrence in pediatric orthotopic liver transplant (OLT) recipients is high and is associated with a high rate of retransplantation (Barshes et al., 2006).

Pediatric recipients of kidney transplants with CHC are another unique population. Again, the prevalence is rare. Data in adults suggest that kidney transplant recipients with CHC have similar graft and patient survival outcomes as do recipients who do not have CHC (Arango et al., 2008). In general, antiviral therapy after renal transplant is not considered a safe option (Pereira et al., 1998). If a decision is made to treat a pediatric kidney or liver transplant recipient who has CHC, extremely close monitoring is mandatory for adverse events due to intolerance of the drugs used and an increased risk for graft rejection when IFN is administered.

Renal Disease (Dialysis)

HCV-infected hemodialysis patients have lower survival rates compared with HCV-positive patients without renal failure because they often present with comorbid diseases and coinfections. Treatment of HCV-positive hemodialysis patients is complex and difficult. Both nephrologists and hepatologists must closely monitor these patients. Patients with CHC on hemodialysis may receive standard or a reduced dose of IFN- α with or without the addition of low-dose ribavirin. IFN- α therapy is modestly effective for the treatment of CHC in patients with end-stage renal disease (Liu & Kao, 2011). Approximately one third of patients can achieve a SVR after conventional or PEG-IFN- α monotherapy. Treatment before renal transplantation is recommended because of the risk of increased graft rejection posttransplant.

Considerations for Patients Cirrhotic at Presentation

Based on both effectiveness and tolerability, therapy has a significantly beneficial effect in patients with compensated cirrhosis, whereas decompensated patients must weigh the risks versus the benefits of treatment. If treatment is to be undertaken in such patients, a low accelerating dose protocol may aid in successfully treating these patients (Everson et al., 2005).

Outcome of Therapy

There are several possible outcomes of HCV therapy. To compare different treatment regimens, it is imperative that standard definitions of

outcomes are used (see Table 9 in the original guideline document). Each outcome has been found to have specific prognostic significance. The interplay between viral dynamics and the host immune response determines viral persistence and the success of treatment. Rapid virological response (RVR) is now considered the strongest predictor of SVR in patients with HCV undergoing antiviral treatment. Patients with an RVR may achieve an SVR using a shorter duration of antiviral treatment. The goal of treatment is to obtain an SVR once therapy is discontinued. Genotype, age, viral load, fibrosis score, and compliance with therapy all affect the likelihood of achieving an SVR.

Definitions:

Grading Systems for Recommendations

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)	Criteria
Strength of Recommendation	
Strong [1]	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak [2]	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption.
Quality of Evidence	
High [A]	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate [B]	Further research may change confidence in the estimate of the clinical effect.
Low [C]	Further research is extremely likely to affect confidence on the estimate of clinical effect.
IMPAACT Pediatrics Grading System	Quality of Evidence for Recommendation
Strength of Recommendation	
A: Strong recommendation for the statement	I: One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	I*: One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes
	II*: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data
	III: Expert opinion

†Studies that include children or adolescents but not studies limited to postpubertal adolescents.

GRADE=Grading of Recommendations, Assessment, Development and Evaluation; IMPAACT=International Maternal Pediatric Adolescent AIDS Clinical Trial

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hepatitis C infection

Guideline Category

Counseling

Diagnosis

Management

Screening

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Nursing

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide details on the epidemiology and natural history of hepatitis C virus (HCV) infection in children, and the diagnostic workup, monitoring and treatment of HCV

Target Population

Pediatric patients (age bracket: 0–18 years) with chronic hepatitis C (CHC) or at risk for hepatitis C virus (HCV) infection living in North America

Note: These guideline do not necessarily to those living in other continents, particularly in developing countries with limited resources for health care.

Interventions and Practices Considered

Assessment/Diagnosis

1. Testing for hepatitis C (HCV) infection (anti-HCV immunoglobulin G [IgG], serum HCV ribonucleic acid [RNA])
2. Monitoring of treatment naive patients
 - Laboratory investigations (serum aminotransferases, bilirubin [total and direct/conjugated], albumin, HCV RNA levels, complete blood count [CBC] with platelet count, and prothrombin time/international normalized ratio [if cirrhosis is present])

- Liver biopsy
3. Screening for hepatocellular carcinoma

Management/Treatment

1. Management of special situations for pediatric HCV infection
2. Interferon- α (IFN- α)
3. Pegylated IFN- α (PEG-IFN- α)
4. Ribavirin
5. Monitoring for adverse effects of therapy
6. Management of specific patient populations

Major Outcomes Considered

- Sustained virological response rate
- Rapid virological response rate
- Early virological response rate
- Partial response rate
- Nonresponse rate
- Relapse rate
- Mortality
- Liver transplant rate
- Adverse event rate
- Sensitivity and specificity of diagnostic tests

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic literature search was performed using accessible databases of relevance: PubMed, MEDLINE, EMBASE, Cochrane Library, Biosis Previews, EBM Reviews, ISI Web of Science, and Scopus including publications from 1990 to January 2011 by the small groups for the selected topics. The search included publications of all of the types presenting or reviewing data on HCV infection in patients younger than 18 years.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

See the "Rating Scheme for the Strength of the Recommendations" field.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

In 2010, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN) developed a pediatric hepatitis C virus (HCV) guidelines working group. Areas of interest were identified, and small groups were assigned to each area. The areas of interest included epidemiology, diagnosis, monitoring, anticipatory guidance and disclosures, treatment, side effects of treatment and monitoring for adverse events, special populations, outcome of therapy, and future therapies.

The strength of recommendations in the Grading of Recommendation Assessment, Development, and Evaluation system was classified as outlined in the "Rating Scheme for the Strength of the Recommendations" field. The Working Group also applied the grading system used by the International Maternal Pediatric Adolescent AIDS Clinical Trial group that allows a comparative ranking between adult and pediatric studies.

Rating Scheme for the Strength of the Recommendations

Grading Systems for Recommendations

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)	Criteria
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IMPAACT Pediatrics Grading System	Quality of Evidence for Recommendation
Strength of Recommendation	
A: Strong recommendation for the statement	I: One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	I*: One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for	II: One or more well-designed, nonrandomized trials or observational cohort studies in children† with

the statement Grading of Recommendations, Assessment, Development and Evaluation (GRADE)	Criteria
	II*: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data
	III: Expert opinion

†Studies that include children or adolescents but not studies limited to postpubertal adolescents.

GRADE=Grading of Recommendations, Assessment, Development and Evaluation; IMPAACT=International Maternal Pediatric Adolescent AIDS Clinical Trial

Cost Analysis

- Cost-effectiveness analysis based on available epidemiological data indicates that screening all of the asymptomatic mothers for chronic hepatitis C (CHC) is not cost-effective; however, mothers at high risk for HCV should be screened for HCV.
- Postrenal transplant use of interferon alfa (IFN- α) has limited efficacy and high cost. It increases the risk of irreversible renal graft rejection in 15% to 64% of cases by promoting the cytotoxic action of T lymphocytes and monocytes, cytokine, and human leukocyte (HLA) antigen production.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

References Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The type of supporting evidence is provided for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment and management of infants, children, and adolescents with hepatitis C virus (HCV) infection

Potential Harms

General Adverse Effects of Treatment

- Constitutional: fever, "flu-like"; fatigue; headache; anorexia; myalgia/arthralgia
- Gastrointestinal: nausea; vomiting; decreased weight
- Blood/lymphatic system: neutropenia; anemia
- Neuropsychiatric: depressed mood/depression; irritability; insomnia/trouble sleeping

- Cutaneous: injection site reaction; rash; alopecia
- Endocrine: thyroid abnormalities; adrenal insufficiency; diabetes
- Ocular: retinopathy; optic neuritis; neuropathy

Special Populations

- The risk of hemolysis due to ribavirin makes combination therapy a complicated issue for patients who have undergone multiple blood transfusions.
- If a decision is made to treat a pediatric kidney or liver transplant recipient who has chronic hepatitis C (CHC), extremely close monitoring is mandatory for adverse events due to intolerance of the drugs used and an increased risk for graft rejection when interferon (IFN) is administered.

Qualifying Statements

Qualifying Statements

The guidelines may need to be adapted to national health care systems because certain tests or treatment regimens may not be available and/or reimbursed by health insurance programs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, Rosenthal P, Schwarz KB. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012 Jun;54(6):838-55. [176 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

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Not stated

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Financial Disclosures/Conflicts of Interest

The authors report no conflicts of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Web site](#)

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Availability of Companion Documents

Supplementary tables are available from the [Journal of Pediatric Gastroenterology and Nutrition Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 7, 2012. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

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